Clin Exp Nephrol (2017) 21:764–770
DOI 10.1007/s10157-016-1364-7

ORIGINAL ARTICLE

Treatment of HCV in renal transplant patients with peginterferon and ribavirin: long-term follow-up

Siu-ka Mak[1] · Ho-kwan Sin[1] · Kin-yee Lo[1] · Man-wai Lo[1] · Shuk-fan Chan[1] · Kwok-chi Lo[1] · Yuk-yi Wong[1] · Lo-yi Ho[1] · Ping-nam Wong[1] · Andrew K. M. Wong[1]

Received: 2 February 2015 / Accepted: 23 November 2016 / Published online: 12 January 2017

Abstract
Background In addition to the observation of an increased viremia among patients with chronic hepatitis C virus (HCV) infection who undergo renal transplantation, fibrosis and necroinflammatory activity have been noted to worsen comparing pre- and post-renal transplantation liver biopsies in some of these patients. Apart from the reported reduced patient and allograft survival rates, post-transplant diabetes mellitus, de novo glomerulonephritis, and an increased overall risk of infection have been observed. However, antiviral therapy for HCV is generally considered contraindicated among patients with solid organ transplants, with the main worry being the risk of acute rejection in relation to the use of interferon. We reported the long-term outcome of four renal transplant patients with chronic HCV infection who received peginterferon-based therapy.
Methods We collected the long-term follow-up data of four patients who completed the therapy with peginterferon in combination with ribavirin. Two of them had renal impairment at baseline.
Results With treatment, they had a significant improvement in terms of serum liver transaminase level, and two patients achieved the early virological response and the other two rapid virological response. All four patients achieved sustained virological response, with neither HCV flare up nor renal dysfunction during follow-up for a mean duration of 74.3 months after therapy.
Conclusions These results suggest that sustained HCV virological response may be achieved without allograft dysfunction, in selected renal transplant patients using a peginterferon-based therapy.

Keywords HCV · Treatment · Peginterferon · Renal transplant · Ribavirin

Introduction

Hepatitis C virus (HCV) infection is one of the leading causes of chronic liver disease [1], death from liver disease, and indication for liver transplantation [2].

While it is known that patient survival is significantly higher in HCV-positive renal transplant patients than in HCV-positive dialysis patients [3], these patients have their own peculiar difficulties when compared with those without the infection. Patients with HCV infection who undergo renal transplantation have reduced survival rates, as do their grafts [4–7]. They are at high risk of developing post-transplant diabetes mellitus [8], as well as de novo glomerulonephritis post-transplantation [9, 10], and, in general, an increased risk of infection [11]. However, antiviral therapy for HCV is generally considered contraindicated among patients with solid organ transplants. This was mainly based on the results of uncontrolled studies where response rates have been unsatisfactory with graft rejection being a consistent problem [12–14]. It has thus been suggested that only HCV-positive patients with fibrosing cholestatic hepatitis [15] should be treated with interferon-based antiviral treatment post-renal transplantation, knowing the much-worsened prognosis in this particular group of patients.

✉ Siu-ka Mak
maksk@ha.org.hk

[1] Renal Unit, Department of Medicine and Geriatrics, Kwong Wah Hospital, 25 Waterloo Road, Kowloon, Hong Kong SAR, China

These previous data are mainly coming from studies looking at patients treated with the conventional interferon rather than peginterferon, with or without ribavirin. Now that we have been using routinely peginterferon, with its better efficacy when compared with the conventional agent, especially when combined with ribavirin, we are desperate to learn more about their long-term efficacy among the renal transplant recipients, acknowledging the evolution of having alternative therapies with greater safety and efficacy than interferon and ribavirin.

We reported the long-term outcome of four successive renal transplant patients with chronic HCV infection who completed the therapy with peginterferon in combination with ribavirin; among the ten such patients, we have encountered during the years from 2006 to 2011. We reported their outcome alongside with five of the six HCV patients who have not received such antiviral therapy, beginning at a time point, which corresponds to the average duration post-transplantation (60 months) before starting antiHCV therapy in the treated group. The other untreated patient not included in the table died of decompensated hepatic failure from chronic active hepatitis at around 4-year post-transplantation. We have followed the recommended doses of peginterferon alfa-2a of 135 μg subcutaneously once weekly, together with ribavirin, 200–800 mg per day in two divided doses for the two patients with renal impairment [16].

Methods

Among 212 renal transplant patients being followed during the period from 2006 to 2011 at our center, 10 patients were found to have chronic HCV infection. For each individual patient, we have considered the liver function, liver biopsy findings, as well as allograft function, history of rejection, and stability of therapeutic drug levels of immunosuppressive therapy, before offering antiviral therapy for HCV. We have explained fully the possible risks and benefits of the antiviral therapy and that of future possible deterioration in liver function. We have stressed the importance of compliance with treatment throughout the expected duration of therapy and tried to reach a joint decision with every individual patient through consensus building. Four patients consented to the therapy and had treatment completed during the period from 2006 to 2011. We are reporting their outcome, alongside with the five (out of the six) HCV patients who have not received such antiviral therapy, beginning at a time point which corresponds to the average duration post-transplantation (60 months) before starting antiHCV therapy in the treated group.

Results

Four renal transplant recipients with chronic HCV infection, transplanted between 2001 and 2007, received the antiviral treatment (Table 1). They were all male and had the cadaveric kidney transplantation performed outside Hong Kong. Three patients had the HCV infection diagnosed after cadaveric renal transplantation, after a mean interval of 18 months (range 1–27). There was no blood transfusion history in our own unit for all patients during the interval between the last negative antiHCV antibody test and the time of diagnosis of HCV infection, though the blood transfusion record during the peri-operative period has not been available to us. The mean age at renal transplantation was 43 years (range 24–55). The mean age at the time of diagnosis of HCV infection was 43.3 years (range 24–58). The mean gap between renal transplantation and antiviral therapy was 61 months (range 38–81), reflecting that these patients had been observed for a period of stable allograft function, before the consideration of antiviral therapy. All patients received triple immunosuppressive therapy (Table 1). The baseline data of five out of the six HCV patients who have not received such antiviral therapy are also presented for comparison, beginning at 60-month post-transplantation, a time point that corresponds to the average duration before starting antiHCV therapy in the treated group. The remaining untreated patient suffered from fatal hepatic failure at around 4 year post-transplantation, and is thus excluded here. Two of these five untreated patients had history of acute rejection early post-transplantation, while the other three patients chose not to receive therapy after thorough deliberation on the risks and benefits.

At baseline before the commencement of antiviral therapy, the mean serum creatinine level was 122 (range 64–169 μmol/l) and none had a history of biopsy proven acute rejection (BPAR). They all were noted to have good drug compliance. Only one of the three patients who had the HCV infection diagnosed post-renal transplantation had a positive antiHCV antibody (Version 4.0, Murex Biotech SA (Pty) Ltd., Kyalami, South Africa), and HCV infection was diagnosed by detection of serum HCV RNA in the other two. The mean serum alanine aminotransferase (ALT) level was about 4 times that of the upper limit of normal (131.5 IU/ml), and the baseline HCV RNA level was at the range of 3.4–8.2 $\times$ 10^6 IU/ml, measured by standardized quantitative real-time polymerase chain reaction assay (detection limit 30 IU/ml, Abbott Laboratories Ltd, Abbott Park, Illinois, USA). The initial viral titre was not available in one patient prior to treatment, though his HCV RNA was positive by PCR and reviewed genotype 1b. Two of these four patients had genotype 1b

Table 1 Characteristics of patients either at the time of HCV treatment, or at the defined time of 60-month post-transplantation for the untreated group

	Treated ($n = 4$)	Untreated ($n = 5$)
Age at transplantation (year)	43 (24–55)	50 (37–68)
Sex (M:F)	4:0	3:2
Cadaveric:living	4:0	5:0
Duration of transplantation before treatment (months)	61 (38–81)	60[a]
Duration of HCV before treatment (months)	61 (10–137)	–
Immunosuppression (no. of patients)		
CyA + MMF + Pred	3	1
FK506 + MMF + Pred	1	1
CyA + Aza + Pred	–	1
mTORi-based	–	1
CyA + Pred	–	1
Serum creatinine (μmol/l)	122 (64–169)	127 (75–209)
Serum alanine aminotransferase (IU/ml)	131.5 (63–256)	46.8 (12–195)
HCV genotype		
1b	2	3
3	2	1
6	–	1
HCV RNA (10^4 IU/ml)	528 (344–820)	358 (183–500)

Aza azathioprine, *CyA* cyclosporine, *MMF* mycophenolate mofetil, *mTORi* mammalian target of rapamycin inhibitor, *Pred* prednisolone

and the other two genotype 3. Liver biopsy was performed on the two patients with 1b genotype and showed features of chronic hepatitis with increased lobular activity (Metavir grade 2 and stage 0) in one, and cirrhosis in the other. The other two patients had declined the offer of liver biopsy. The baseline renal function of the untreated group was quite comparable to the treated patients, though numerically; the untreated patients had a slightly lower average viral load and ALT level (Table 1).

We have followed the recommended doses of peginterferon alfa-2a (Pegasys®, F. Hoffmann-La Roche Ltd., Basel, Switzerland) of 135 μg subcutaneously once weekly, together with ribavirin (Copegus®, Patheon Inc., Mississauga, Canada) at 200–800 mg per day in two divided doses, starting low and titrating up slowly as long as side-effects were manageable [16], for the two patients with significant renal impairment. All four patients had cytopenia that required either ribavirin dose reduction or temporary cessation of the agents for 1–2 weeks. The trough total peripheral white blood cell and platelet counts were 1.5–2.6 × 10^9/l and 73–106 × 10^9/l, respectively. These were not associated with any clinical consequences and were transient. The anemia responded to erythropoiesis-stimulating agents given in three patients. Only one patient complained of flu symptoms at the initial phase of therapy, but he could manage to complete the whole course of therapy.

With this combination antiviral therapy, there was a significant improvement in terms of serum ALT level, and two patients achieved the early virological response (defined as a ≥2 log reduction compared with the baseline level or complete absence of serum HCV RNA at week 12 of therapy, both genotype 1b) and the other two rapid virological response (defined as undetectable serum HCV RNA at week 4 of therapy, both genotype 3). All four achieved sustained virological response (SVR, defined as continued absence of detectable serum HCV RNA at week 12 after completion of therapy), with neither HCV flare nor renal dysfunction during follow-up for a mean duration of 74.3 months after therapy (Tables 2, 3). In contrast, the HCV RNA level has increased over the duration of follow-up, not to mention the one patient with fatal hepatic failure at around 4-year post-transplantation. In addition, there was a trend towards a higher serum creatinine level, including one who was back to dialysis therapy after failed allograft due to chronic antibody-mediated rejection. This contrasts with the slight renal function improvement among the treated patients.

Discussion

Similar to hepatitis B virus, there is evidence that HCV has a direct role in carcinogenesis [17], not to mention its specific relationship with proteinuria [18], metabolic abnormalities [19], including steatosis, insulin resistance, type 2 diabetes, as well as extrahepatic diseases like mixed cryoglobulinemia [18]. Among HCV-positive patients in

Table 2 Mean blood parameters and hepatitis C virus RNA at different stages of therapy or at the same time points counted from 60-month post-transplantation for the untreated group

	Baseline	12-week Rx	24-week Rx	48-week Rx[a]	24-week post-Rx	At last follow-up
Treated ($n = 4$)						
AST (IU/ml)	51.3	61.8	54	39	20.5	17
ALT (IU/ml)	51	45.3	53.5	41.5	19.5	15.3
Bilirubin (μmol/l)	18.5	17.8	15.3	13	14.8	11.3
HCV RNA (10^4 IU/ml)	528	All UD	All UD	All UD	All UD	All UD
WBC (10^9/l)	5.4	2.8	2.6	3	6.3	6
Hemoglobin (g/dl)	12.3	9.7	10.4	11.5	13.9	12.9
Platelets (10^9/l)	172.8	149.3	147.3	114.5	188.8	179.8
Creatinine (μmol/l)	122	125.8	107.5	127.5	109	107
eGFR (ml/min/1.73 m^2)	67.1	65.3	72.8	55.5	69.4	72.1
Untreated ($n = 5$)						
AST (IU/ml)	30	31.2	27.6	36.2	34.6	21.4
ALT (IU/ml)	46.8	67	60.5	68.2	74.6	24.7
Bilirubin (μmol/l)	19	20.4	16.6	14.8	15.2	15.2
HCV RNA (10^4 IU/ml)	358	349	339	373	853	2607
WBC (10^9/l)	5.9	6.1	6.4	6.2	7.1	6.6
Hemoglobin (g/dl)	12.9	12.6	11.9	11.8	12.3	11.4
Platelets (10^9/l)	235.2	253.0	251.4	254.0	262.8	220.6
Creatinine (μmol/l)	127.0	129.2	134.4	139.6	146.2	544.8[b]
eGFR (ml/min/1.73 m^2)	57.4	55.1	54.7	51.1	51.5	32.6[b]

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *eGFR* estimated glomerular filtration rate, *HCV* hepatitis C virus, *UD* undetected, *WBC* white blood cells count

[a] For the 2 patients with genotype 1b

[b] Including a patient back to dialysis after failed allograft due to chronic antibody-mediated rejection

Table 3 Improvement in liver enzymes and hepatitis C virus RNA at different stages of therapy and follow-up

	Baseline	24-week Rx	48-week Rx	24-week post-Rx	At last follow-up
No. of patients with normal AST	1	3	3	4	4
No. of patients with normal ALT	1	2	3	4	4
No. of patients with undetectable HCV RNA	–	4	4	4	4

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *HCV* hepatitis C virus

the general population, the risk of developing cirrhosis varies from 5 to 25% over periods of 25–30 years [20, 21]. This progression may be accelerated in persons who are immunosuppressed [22], though the available prospective studies assessing liver histology in HCV-positive renal transplant recipients revealed controversial results [23–26]. Concurring with the observation of the increased viremia among these patients [27, 28], Uehara et al. observed that fibrosis worsened in 50% of the patients, while necroinflammatory activity worsened in 32%, when comparing pre- and post-renal transplantation liver biopsies [29]. The use of immunosuppressive therapy might also play a role in the liver disease progression [30].

Three of our four patients had the HCV infection diagnosed after cadaveric renal transplantation, and with only a lapse of 10–65 months, their liver function had already been impaired significantly. Liver biopsy in two of them showed evidence of chronic hepatitis or cirrhosis. In our institution, we routinely screened for antiHCV post-transplantation, for twice in the first 6 months. However, the exact timing of the infection could not be ascertained as two of the four patients were negative for antiHCV post-transplantation and the infection was only picked up by detection of serum HCV RNA, echoing the experience by others in the context of immunosuppressed status [31]. We could not ascertain the source of the HCV infection, be it

from the transplant organ or peri-operative blood transfusion, or through alternative routes, as a result of the lack of transplantation and operation records, though we have no history of blood product transfusion in our own unit for all these patients, the confidence from the universal screening for HCV in the local Red Cross service aside.

The search for newer antiviral regimens targeting HCV is progressing nonstop with many different agents in trial, including agents derived from current treatment (e.g., taribavirin, a liver-targeted formulation of ribavirin), and those that are targeting at HCV-encoded proteins (e.g., the NS3/4A protease, the NS5A nonstructural proteins, and the NS5B RNA-dependent RNA polymerase) or host-encoded proteins. All oral combinations of these agents are now possible, e.g., daclatasvir, an NS5A protein inhibitor, and asunaprevir, an NS3/4A serine protease inhibitor, have been shown to be highly effective even in unfavorable settings [32]. However, the newer direct acting antiviral (DAA) agents are yet to be affordable in most countries, despite the positive results from the early clinical studies and updated guidelines [33], and thus, peginterferon and ribavirin therapy have remained the core treatment commonly used clinically. For the general population, the currently recommended duration of therapy for chronic HCV infection with the combination of a peginterferon alfa and ribavirin should be based on the viral genotype and the initial response to treatment [34].

Referring to the 2009 American Association for the Study of Liver Diseases guideline, patients with solid organ transplants are among the group for whom antiviral therapy is generally considered contraindicated [34]. This was based on the results of uncontrolled studies looking at patients treated with the conventional interferon, with or without ribavirin where response rates have been low and yet graft rejection being a consistent problem, with rates up to 71.7% [12–14]. These findings were likely influenced by the type of immunosuppression regimen used, timing of treatment in relation to transplantation, mixture of different genotypes of the HCV, liver status at the time of treatment, as well as host factors like recipient age [30]. Interferon increases the expression of cytokine genes and surface expression of human leukocyte antigens, and may result in production of donor-specific alloantibodies and increase the likelihood of humoral-mediated rejection [35]. It has thus been suggested that only patients with fibrosing cholestatic hepatitis [15], progressive HCV-associated glomerulopathy [36], or life-threatening vasculitis [37] should be treated with interferon-based antiviral treatment post-renal transplantation. However, such an approach might have forfeited the best occasion to eradicate HCV, as severe fibrosis and cirrhosis have been proven to be negative predictors of SVR [38].

In the context of an immunosuppressed state, the observed increased viremia among renal transplant patients [27, 28] may theoretically be associated with a lower chance to achieve an SVR [34, 39]. However, there are some recent data revealing the possible association between the use of immunosuppressive regimens and beneficial effects on necroinflammatory activity of HCV-related liver disease, or even an improved patient survival [30]. In a meta-analysis of 102 renal transplant recipients with HCV infection treated with the conventional interferon-based therapy, the efficacy in terms of achieving SVR was only 18%, a figure inferior to the reported one for the non-transplant general population; while the drop-out rate was 35% [40].

The long-acting pegylated IFN may supposedly have a higher risk of inducing acute rejection [36]. Pegylation has also made interferon less susceptible to renal clearance than the conventional agent [41], it has generally been recommended to use reduced doses in patients with moderate-to-advanced renal failure [42]. Pageaux et al. reported the low risk of renal dysfunction, acceptable tolerance, and significant virological efficacy among 8 renal transplant patients treated with peginterferon, with or without ribavirin [43]. Aljumah et al. reported a 5.3% incidence of acute rejection or chronic allograft nephropathy in 19 patients similarly treated [44]. Sanai et al. studied the same in 32 renal transplant recipients of more than 12-month duration [45]. None of the patients with incremental and sustained serum creatinine increases (6.3%) had BPAR, and this compared favorably to 16.1% among untreated historical controls. Among non-cirrhotic patients, SVR was achieved in 46.2%, but none of the cirrhotic patients obtained an SVR. This contrasts significantly with the overall SVR rate of 56–94% (depending on EVR and HCV viral load) generally expected from the use of peginterferon and ribavirin in the general population without kidney transplantation [34, 45]. In the three studies involving 59 patients in the meta-analysis by Wei et al. [46], using peginterferon plus ribavirin, the overall SVR rate was 40.6%, comparing favorably with the 20.9% observed in patients given standard interferon-based therapy. The overall allograft rejection rate among whole cohort (both therapies combined) was 4%.

While liver biopsy has widely been regarded as the "gold standard" for defining the liver disease status, it has risks [47] and is subject to sampling error [48]. The role of biopsy for defining the fibrosis stage, even in patients with genotype 1 infection, is at present in a state of flux and possible transition [34]. We have offered the antiviral therapy to two patients who declined liver biopsy when they accepted the therapy in light of the possible evolution of HCV infection in their context of an immunosuppressed state.

In our series with long-term follow-up, the good SVR achieved without allograft dysfunction only refers to genotypes 1 and 3, the two common types in both Asia and globally. The results might not be generalizable to patients with other HCV genotypes. Treatment of chronic HCV infection in the first year after transplantation may increase the risk for acute rejection [35, 39]. Antiviral therapy might be safer if given years after transplantation and in patients with stable graft function, no history of rejection [49, 50], and have therapeutic drug levels of immunosuppressive therapy. Following all these recommendations religiously, we have highly selected the group of HCV-positive renal transplant patients for consideration of therapy, excluding patients with higher than normal immunological risk, except for one patient with his second transplantation, acknowledging his deteriorating liver function and aggressive liver biopsy findings. This patient with cirrhosis responded to therapy achieving SVR along with the other non-cirrhotic patients. They all did not have history of BPAR and renal function had been observed to be stable, and treatment was started at 38–81 months after the transplantation. We have also witnessed good compliance to therapy despite the side-effects experienced, including the brief cytopenia that required timely dose titration, and flu-like discomfort. We have had no drop-outs and the scheduled duration of therapy was duly completed. All these would have contributed to the successful achievement of SVR without allograft dysfunction.

Though not being practiced at our center at the time the antiviral therapy was offered to this group of patients, there have been other measures that would allow a better assessment of the immunological risk before consideration of therapy. Protocol allograft biopsy would help to rule out sub-clinical rejection [37]. The measurement of serum donor-specific HLA antibody would allow detection of antibodies against unacceptable antigens, and thus help predict the future immunological risks associated with therapy. An ever-expanding array of biomarkers, from gene expression, genomics, proteomics and metabolomics, obtained from blood, urine, or kidney tissue is becoming a powerful diagnostic tool to predict transplant outcomes [51].

The decision to treat a renal transplant patient with interferon-based antiviral therapy must be individualized. While there is still a paucity of data in this special group of patients, the current evolution towards DAA-based therapy that can at the same time avoid drug–drug interactions with immunosuppressive drugs for renal transplant recipients might serve the ultimate solution. Indeed, the newest AASLD guideline has already included organ transplant recipients among patients being given the highest priority for HCV treatment because of the high risk for severe complications [33], financial implications aside.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the hospital research ethics committee (approval number KW/EX-13-077) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards

Conflict of interest None.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Williams R. Global challenges in liver disease. Hepatology. 2006;44:521–6.
2. Kim WR. The burden of hepatitis C in the US. Hepatology. 2002;36(5 Suppl 1):S30–4.
3. Knoll GA, Tankersley MR, Lee JY, Julian BA, Curtis JJ. The impact of renal transplantation on survival in hepatitis C positive end-stage renal disease patients. Am J Kidney Dis. 1997;29:608–14.
4. Bruchfeld A, Wilczek H, Elinder CG. Hepatitis C infection, time in renal replacement therapy, and outcome after kidney transplantation. Transplantation. 2004;78:745–50.
5. Aroldi A, Lampertico P, Montagnino G, Passerini P, Villa M, Campise MR, Lunghi G, Tarantino A, Cesana BM, Messa P, Ponticelli C. Natural history of hepatitis B and C in renal allograft recipients. Transplantation. 2005;79:1132–6.
6. Maluf DG, Fisher RA, King AL, Gibney EM, Mas VR, Cotterell AH, Shiffman ML, Sterling RK, Behnke M, Posner MP. Hepatitis C virus infection and kidney transplantation: predictors of patient and graft survival. Transplantation. 2007;83:853–7.
7. Mathurin P, Mouquet C, Poynard T, Sylla C, Benalia H, Fretz C, Thibault V, Cadranel JF, Bernard B, Opolon P, Coriat P, Bitker MO. Impact of hepatitis B and C virus on kidney transplantation outcome. Hepatology. 1999;29:257–63.
8. Fabrizi F, Martin P, Dixit V, Bunnapradist S, Kanwal F, Dulai G. Post-transplant diabetes mellitus and HCV seropositive status after renal transplantation: meta-analysis of clinical studies. Am J Transplant. 2005;5:2433–40.
9. Roth D, Cirocco R, Zucker K, Ruiz P, Viciana A, Burke G, Carreno M, Esquenazi V, Miller J. De novo membranoproliferative glomerulonephritis in hepatitis C virus-infected renal allograft recipients. Transplantation. 1995;59:1676–82.
10. Floege J. Recurrent glomerulonephritis following renal transplantation: an update. Nephrol Dial Transplant. 2003;18:1260–5.
11. Pereira BJ, Natov SN, Bouthout BA, Murthy BV, Ruthazer R, Schmid CH, Levey AS. Effect of hepatitis C infection and renal transplantation on survival in end-stage renal disease. The New England Organ Bank Hepatitis C Study Group. Kidney Int. 1998;53:1374–81.
12. Rostaing L, Izopet J, Baron E, Duffaut M, Puel J, Durand D. Treatment of chronic hepatitis C with recombinant interferon alpha in kidney transplant recipients. Transplantation. 1995;59:1426–31.
13. Shu KH, Lan JL, Wu MJ, Cheng CH, Chen CH, Lee WC, Chang HR, Lian JD. Ultralow-dose alpha-interferon plus ribavirin for the treatment of active hepatitis C in renal transplant recipients. Transplantation. 2004;77:1894–6.
14. Sharma RK, Bansal SB, Gupta A, Gulati S, Kumar A, Prasad N. Chronic hepatitis C virus infection in renal transplant: treatment and outcome. Clin Transplant. 2006;20:677–83.
15. Toth CM, Pascual M, Chung RT, Graeme-Cook F, Dienstag JL, Bhan AK, Cosimi AB. Hepatitis C virus-associated fibrosing

cholestatic hepatitis after renal transplantation: response to interferon-alpha therapy. Transplantation. 1998;66:1254–8.
16. Kidney Disease: Improving Global Outcomes, KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of Hepatitis C in chronic kidney disease. Kidney Int. 2008;73(Suppl 109):S1–99.
17. Lemon SM, McGivern DR. Is hepatitis C virus carcinogenic? Gastroenterology. 2012;142:1274–8.
18. Fabrizi F, Martin P, Dixit V, Messa P. Hepatitis C virus infection and kidney disease: a meta-analysis. Clin J Am Soc Nephrol. 2012;7:549–57.
19. Negro F. HCV infection and metabolic syndrome: which is the chicken and which is the egg? Gastroenterology. 2012;142:1288–92.
20. Liang TJ, Rehermann B, Seeff LB, Hoofnagle JH. Pathogenesis, natural history, treatment, and prevention of hepatitis C. Ann Intern Med. 2000;132:296–305.
21. Seeff LB. Natural history of chronic hepatitis C. Hepatology. 2002;36(5 Suppl 1):S35–46.
22. Sulkowski MS. The HIV-coinfected patient: managing viral hepatitis. J Acquir Immune Defic Syndr. 2007;45(Suppl 2):S36–7.
23. Alric L, Di-Martino V, Selves J, Cacoub P, Charlotte F, Reynaud D, Piette JC, Péron JM, Vinel JP, Durand D, Izopet J, Poynard T, Duffaut M, Rostaing L. Long-term impact of renal transplantation on liver fibrosis during hepatitis C virus infection. Gastroenterology. 2002;123:1494–9.
24. Zylberberg H, Nalpas B, Carnot F, Skhiri H, Fontaine H, Legendre C, Kreis H, Bréchot C, Pol S. Severe evolution of chronic hepatitis C in renal transplantation: a case control study. Nephrol Dial Transplant. 2002;17:129–33.
25. Roth D, Gaynor JJ, Reddy KR, Ciancio G, Sageshima J, Kupin W, Guerra G, Chen L, Burke GW 3rd. Effect of kidney transplantation on outcomes among patients with hepatitis C J Am Soc Nephrol. 2011;22:1152–60.
26. Kamar N, Alric L, Izopet J, Rostaing L. Hepatitis C virus and kidney disease. Clin Res Hepatol Gastroenterol. 2013;37:328–33.
27. Rostaing L, Izopet J, Sandres K, Cisterne JM, Puel J, Durand D. Changes in hepatitis C virus RNA viremia concentrations in long-term renal transplant patients after introduction of mycophenolate mofetil. Transplantation. 2000;69:991–4.
28. Pereira BJ, Levey AS. Hepatitis C virus infection in dialysis and renal transplantation. Kidney Int. 1997;51:981–99.
29. de Oliveira Uehara SN, Emori CT, da Silva Fucuta Pereira P, Perez RM, Pestana JO, Lanzoni VP, e Silva IS, Silva AE, Ferraz ML. Histological evolution of hepatitis C virus infection after renal transplantation. Clin Transplant. 2012;26:842–8.
30. Li LF, Shi KQ, Lin YQ, Wang LR, He JP, Braddock M, Chen YP, Zheng MH. Factors associated with efficacy of pegylated interferon-α plus ribavirin for chronic hepatitis C after renal transplantation. Gene. 2014;544:101–6.
31. Chan TM, Lok AS, Cheng IK, Chan RT. A prospective study of hepatitis C virus infection among renal transplant recipients. Gastroenterology. 1993;104:862–8.
32. Manns M, Pol S, Jacobson IM, Marcellin P, Gordon SC, Peng CY, Chang TT, Everson GT, Heo J, Gerken G, Yoffe B, Towner WJ, Bourliere M, Metivier S, Chu CJ, Sievert W, Bronowicki JP, Thabut D, Lee YJ, Kao JH, McPhee F, Kopit J, Mendez P, Linaberry M, Hughes E, Noviello S, HALLMARK-DUAL Study Team. All-oral daclatasvir plus asunaprevir for hepatitis C virus genotype 1b: a multinational, phase 3, multicohort study. Lancet. 2014;384:1597–605.
33. AASLD/IDSA HCV guidance panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology. 2015;62:932–54.
34. Ghany MG, Strader DB, Thomas DL, Seeff LB. AASLD practice guidelines: diagnosis, management, and treatment of Hepatitis C: an update. Hepatology. 2009;49:1335–74.
35. Baid S, Tolkoff-Rubin N, Saidman S, Chung R, Williams WW, Auchincloss H, Colvin RB, Delmonico FL, Cosimi AB, Pascual M. Acute humoral rejection in hepatitis C infected renal transplant recipients receiving antiviral therapy. Am J Transplant. 2003;3:74–8.
36. Terrault NA, Adey DB. The kidney transplant recipient with hepatitis C infection: pre- and posttransplantation treatment. Clin J Am Soc Nephrol. 2007;2:563–75.
37. KDIGO Clinical practice guideline for the care of kidney transplant recipients. Am J Transplant. 2009;9(suppl 3):S1–S155.
38. Teoh NC, Farrell GC, Chan HL. Individualisation of antiviral therapy for chronic hepatitis C. J Gastroenterol Hepatol. 2010;25:1206–16.
39. Zheng MH, Chen YP. Long-term pegylated interferon-α-2a treatment for chronic hepatitis C in an elderly renal transplant recipient: case report and literature review. Medicine. 2015;94:e390.
40. Fabrizi F, Lunghi G, Dixit V, Martin P. Meta-analysis: anti-viral therapy of hepatitis C virus-related liver disease in renal transplant patients. Aliment Pharmacol Ther. 2006;24:1413–22.
41. Gupta SK, Pittenger AL, Swan SK, Marbury TC, Tobillo E, Batra V, Sack M, Glue P, Jacobs S, Affrime M. Single-dose pharmacokinetics and safety of pegylated interferon-alpha2b in patients with chronic renal dysfunction. J Clin Pharmacol. 2002;42:1109–15.
42. Baid-Agrawal S, Pascual M, Moradpour D, Frei U, Tolkoff-Rubin N. Hepatitis C virus infection in haemodialysis and kidney transplant patients. Rev Med Virol. 2008;18:97–115.
43. Pageaux GP, Hilleret MN, Garrigues V, Bismuth M, Audin-Mamlouk H, Zarski JP, Mourad G. Pegylated interferon-α-based treatment for chronic hepatitis C in renal transplant recipients: an open pilot study. Transpl Int. 2009;22:562–7.
44. Aljumah AA, Saeed MA, Al Flaiw AI, Al Traif IH, Al Alwan AM, Al Qurashi SH, Al Ghamdi GA, Al Hejaili FF, Al Balwi MA, Al Sayyari AA. Efficacy and safety of treatment of hepatitis C virus infection in renal transplant recipients. World J Gastroenterol. 2012;18:55–63.
45. Sanai FM, Mousa D, Al-Mdani A, Al-Shoail G, Al-Ashgar H, Al Meshari K, Al-Qahtani A, Saadeh M, Bzeizi KI, Aleid H. Safety and efficacy of peginterferon-α2a plus ribavirin treatment in renal transplant recipients with chronic hepatitis C. J Hepatol. 2013;58:1096–103.
46. Wei F, Liu J, Liu F, Hu H, Ren H, Hu P. Interferon-based antiviral therapy for hepatitis C virus infection after renal transplantation: an updated meta-analysis. PLoS One. 2014;9:e90611.
47. Dienstag JL. The role of liver biopsy in chronic hepatitis C. Hepatology. 2002;36(5 Suppl 1):S152–60.
48. Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, Pyrsopoulos NT, Feng ZZ, Reddy KR, Schiff ER. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol. 2002;97:2614–8.
49. Durlik M, Gaciong Z, Rowińska D, Rancewicz Z, Lewandowska D, Kozłowska B, Wyzgał J, Soluch L, Walewska-Zielecka B, Rowiński W, Lao M. Long-term results of treatment of chronic hepatitis B, C and D with interferon-alpha in renal allograft recipients. Transpl Int. 1998;11(Suppl 1):S135–9.
50. Luciani G, Bossola M, Muscaritoli M, Panocchia N, Ferrante A, Nanni G, Piccioni E, Tazza L, Grillo RL, Rossi Fanelli F, Castagneto M. Sustained response with negative serum HCV-mRNA and disappearance of antibodies after interferon-alpha therapy in a kidney transplant recipient with chronic active viral hepatitis C. J Nephrol. 2003;16:417–20.
51. Ong S, Mannon RB. Genomic and proteomic fingerprints of acute rejection in peripheral blood and urine. Transplantation reviews. 2015;29:60–7.